Refer to: Whipple's disease—Medical Staff Conference, University of California, San Francisco. West J Med 125:479-484, Dec 1976

Medical Staff Conference

Whipple's Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. MORRELLI:* *This year has been marked by excellence in teaching and in management of the difficult responsibilities that fall to the chief residents. One of our chiefs, Dr. Frank Yang, will present for us now a discussion of Whipple's disease.*

Case Summary

DR. YANG:† A 63-year-old white woman of Italian origin was referred to the General Clinical Research Center at the University of California San Francisco Medical Center in May 1975 for evaluation of hypocalcemia. Her illness began in 1967 when intermittent polyarthralgias developed. Five years later she noted onset of diarrhea (characterized by chalky, bulky stools) and progressive weight loss. In March 1974 shortly after arrival in California she was admitted to hospital with severe diarrhea complicated by pneumonia. It was incidentally noted that she was severely hypocalcemic. The pneumonia responded dramatically to therapy with penicillin and she subsequently gained 30 pounds in weight.

In August 1974 the serum calcium level was normal. In March 1975 (one year following the penicillin treatment), however, she noted a recurrence of diarrhea, and in addition abdominal bloating and weight loss. In April 1975 she once again was found to be severely hypocalcemic. Treatment with vitamin D and calcium was only partially effective. She denied any fever along with her illness, her past medical history was significant only for Parkinson's disease treated for many years with trihexyphenidyl hydrochloride (Artane®) and L-dopa.

On physical examination the patient was cachectic and had mask facies. Blood pressure was 100/60 mm of mercury, pulse 90 beats per minute and the patient was afebrile. The skin was hyperpigmented and a mild glossitis was noted. There was no lymphadenopathy. Findings on chest and cardiovascular examinations were normal. The abdomen was distended, and doughy, but was otherwise normal. The stool guaiac was 3+ positive for occult blood. Trace pedal edema was noted bilaterally. The joints were found to be normal. On neurological examination a resting tremor and slight cogwheel rigidity were the only abnormalities noted.

On admission, the hemoglobin value was 11.3 grams per dl and the hematocrit reading was 33 percent with microcytic and hypochromic indices (mean corpuscular volume [MCV] 77, mean corpuscular hemoglobin [MCH] 26.1, mean corpus-

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ABBREVIATION USED IN TEXT
PAS = periodic acid-Schiff

cular hemoglobin concentration [MCHC] 33.8). The leukocyte count was 6,800 with a normal differential; prothrombin time was 12.6 seconds (control 11.9 seconds). Laboratory studies gave the following values: sodium, 134 mEq per liter; potassium, 3.5 mEq per liter; chloride 96 mEq per liter; bicarbonate, 27 mEq per liter; glucose, 91 mg per dl; serum calcium, 6.6 mg per dl; phosphorus 3.8 mg per dl; alkaline phosphatase, 132 IU per liter; serum glutamic oxaloacetic transaminase (SGOT), lactic acid dehydrogenase (LDH) and bilirubin all within normal limits; serum albumin, 2.9 grams per dl; cholesterol, 124 mg per dl; carotene, 14 μg per dl; serum iron, 32; total iron-binding capacity (TIBC), 310; B_{12}, 700 picograms per ml and folate was 20 nanograms per ml. Results on antinuclear antibody (ANA) and lupus erythematosus (LE) tests and on a Venereal Disease Research Laboratories study (VDRL) were all negative. Other values were: serum cortisol, 21.7 μg per dl; T_3 uptake, 31 percent; T_4, 9 μg per dl; IgG, 850 mg per dl; IgM, 70 mg per dl, and IgA 132 mg per dl. Stool smear showed occasional polymorphonuclear cells. Stool specimens for culture and for examination for ova and parasites were negative for pathogens. Findings on analysis of urine were unremarkable.

An x-ray film of the chest showed osteopenia but no active cardiopulmonary disease. A kidney, ureter, bladder x-ray study showed a dilated loop of small bowel with air-fluid levels on upright examination. Radiographic examination of the small bowel showed thickened mucosa generally. Electrocardiographic findings included a left anterior heart block, diffusely low T waves and prolonged Q-T interval. There was no urinary excretion of D-xylose after oral ingestion of 5 grams. A 72-hour stool fat collection—with the patient receiving a diet yielding 100 grams of fat per day—showed total fat excretion of 240 grams.

Results of a small bowel biopsy study showed typical changes of Whipple's disease with foamy macrophages in the lamina propria; periodic acid-Schiff (PAS) stain was strongly positive. Treatment was begun with penicillin, 1.2 million units given intramuscularly, and streptomycin, 1 gram administered intramuscularly each day for ten days. This was followed by tetracycline, 250 mg given orally four times a day for a year. There was prompt response to treatment with resolution of gastrointestinal symptoms and steady weight gain. When last seen, the patient was asymptomatic, had gained 30 pounds and the laboratory measures of malabsorption had returned to normal.

TABLE 1.—*Incidence of Major Symptoms in Whipple's Disease*

Major Symptoms	*Incidence (Percent)*
Arthralgia	70 to 90
Abdominal pain	70
Diarrhea	80
Weight loss	95

Discussion

Our patient today presents as a typical case of Whipple's disease. Perhaps the only unusual feature is that the patient is female. Whipple's disease was named after Dr. George White Whipple, who was an instructor in pathology at Johns Hopkins. There he encountered a 36-year-old physician with gradual loss of weight and strength. Specimens of the patient's stool were found to consist chiefly of neutral fat and fatty acids. Indefinite abdominal pain and a peculiar multiple arthritis were present. He reported this case in 1907,[1] emphasizing the anatomical finding of deposition of fat and fatty acids in the intestinal and mesenteric tissues. The disease was called intestinal lipodystrophy and was thought for a while to be a storage disease. Whipple also described a foamy cell found in the intestinal mucosa and the mesenteric lymph nodes. This foamy cell, which is now recognized as the hallmark of the disease, has been studied at length since then, especially by the use of electron microscopy in the early 1960's. The results have led to a new understanding of the cause and pathogenesis of this disease.

Several excellent reviews have been published in the recent literature on Whipple's disease.[2-4] It is a rare disorder: Miskasche and co-workers reviewed the world's literature in 1974 and found less than 250 reported cases. Patients with Whipple's disease are predominately male (90 percent of the reported cases). The disease affects mostly Caucasians and all of the cases seem to be reported in the United States and continental Europe. Only one American Indian and three black patients are reported in the literature. The peak incidence is in the fifth and sixth dec-

TABLE 2.—*Incidence of Major Physical Findings in Whipple's Disease**

Physical Finding	*Number of Patients*	*Percent*
Hypotension	140	58
Peripheral lymph nodes	111	46
Skin pigmentation	103	43
Fever	85	35
Peripheral edema	73	30
Abdominal tenderness	124	52
Abdominal distention	102	43
Abdominal mass	51	21
Ascites	26	11
Glossitis	37	15
Splenomegaly	14	6

*From Mikasche LW, Blümcke S, Fritsche D, et al.[4]

TABLE 3.—*Incidence of Abnormal Laboratory Findings in Whipple's Disease*

Abnormal Laboratory Findings	*Incidence (Percent)*
Anemia (hypochromic)	83
Hypoalbuminemia	85
Hypokalemia	45
Hypocalcemia	63
Hypocholesterolemia	60
Steatorrhea	93
Decreased D-xylose absorption	78

ades. The disease, however, has been reported in a 3-month-old baby who presented as "failure to thrive."[5]

Table 1 illustrates the major symptoms of this disease. In the early stages, arthralgia is the most prominent symptom and occurs in 70 to 90 percent of all patients. This may precede the diagnosis by from 1 to 35 years. Usually the pain is mild and migratory. Inflammatory changes of the joints are occasionally described, but joint deformity is rare. Ankles, knees, shoulders and wrists are most frequently involved, but any joint may be affected. Spondylitis has been reported, but is usually asymptomatic and is noted incidently on x-ray studies as mild arthritic changes in the sacroiliac joints. Other important early symptoms include fatigue, anorexia and fever. Fever occurs in about 40 percent of patients and can present as a fever of unknown origin. The fever generally is low grade, but occasionally can be spiking.

The diagnosis of Whipple's disease is rarely made during the early stages. By the time patients seek medical care and a diagnosis is made, the disease has entered the late stage when intestinal symptoms predominate. Nonspecific abdominal pain, usually epigastric, and postprandial bloating are noted in about 70 percent of the patients. This is followed by diarrhea (either watery or steatorrheic), as in our patient today. Gross gastrointestinal bleeding is unusual, but occult blood loss is frequent. At this stage weight loss is invariable, averaging 20 to 30 pounds, but a weight loss as great as 100 pounds has been observed. The arthralgia may improve or even disappear during this intestinal phase for reasons that are unclear. If no treatment is offered, the patient eventually dies from malnutrition and cachexia.

Table 2 is a summary of the physical findings based on 238 patients reported in the literature.[4] Mild hypotension is a relatively frequent finding. This, along with increased skin pigmentation and fever, has frequently led to the mistaken diagnosis of adrenal insufficiency. Although the adrenal glands can be involved histologically, adrenal functions are normal in those cases studied. In our patient the serum cortisol value was within normal limits.

In about half of the patients moderate peripheral lymphadenopathy is present. Abdominal examination generally shows diffuse tenderness and distention. Occasionally enlarged mesenteric lymph nodes may present as palpable masses. Ascites is unusual and may be chylous in nature. Finally, splenomegaly is a rare finding in this disease.

Table 3 summarizes the laboratory findings, which generally reflect malabsorption. Nonspecific anemia is seen frequently. Since in these patients malabsorption of vitamin B_{12} or folate usually is not present, megaloblastic changes are uncommon. In our patient both serum B_{12} and folate levels were normal.

Hypoalbuminemia is frequently seen and probably is due, in part, to gastrointestinal protein loss. Laster and associates[6] injected radioactive albumin into patients with Whipple's disease and were able to recover significantly greater amounts in stool specimens than were found in those of normal controls. This abnormality corrects rapidly with treatment. In addition, a lower albumin turnover rate occurs in these patients indicating impairment in the synthesis of albumin.

The hypocalcemia and elevated alkaline phosphatase are consistent with osteomalacia secondary to steatorrhea and malabsorption. Steatorrhea is almost uniformly present in the late stages of the disease and sometimes can be extreme. D-xylose absorption is also abnormal in about 80 percent of the patients.

The definitive diagnosis of Whipple's disease is

made by showing the presence of PAS-positive macrophages in the mucosa of small bowel which can be easily obtained by per-oral small intestinal biopsy.

Figures 1 and 2 illustrate the typical histological changes seen on a biopsy study of the small bowel. The villi are blunted in severe cases, but the hallmark of the disease is infiltration of the lamina propria with foamy macrophages which stain positively with PAS stain. These macrophages may also be found in the mesenteric lymph nodes and, in fact, in many other tissues in the body.

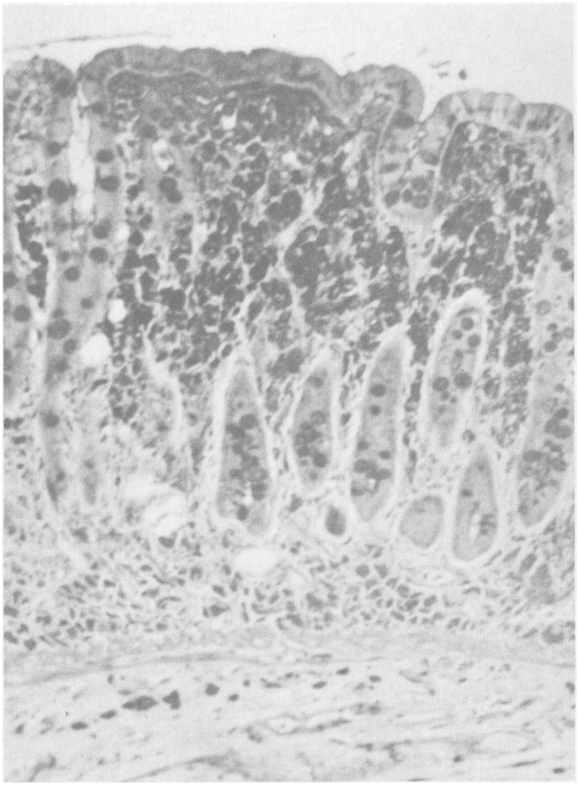

Figure 1.—Small bowel biopsy specimen stained with periodic acid-Schiff stain showing many PAS-positive macrophages.

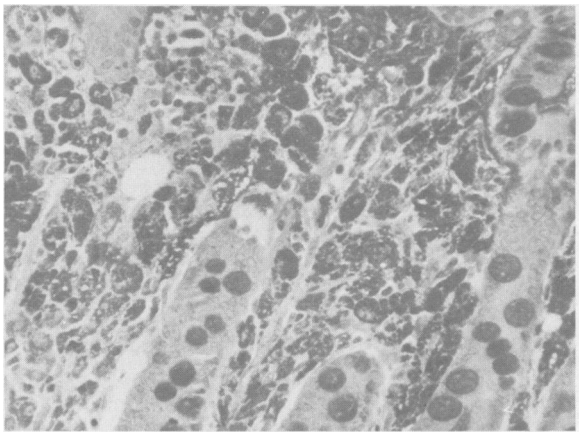

Figure 2.—Close-up of macrophages laden with PAS-positive material.

The colon and rectum can be involved but one must be careful in interpreting the presence of PAS-positive macrophages in the rectal mucosa since this can be a normal finding. The fact that Whipple's disease is a systemic disease is usually not emphasized. Peripheral lymph nodes are frequently involved and sometimes serve to confirm the diagnosis. Occasionally the histology of lymph nodes can suggest sarcoid or lymphoma. Cardiac involvement is frequently found at autopsy. For example, pericarditis is present in about 80 percent and endocarditis involving the mitral and aortic valves in about 25 percent of the cases. However, clinical symptoms attributable to these lesions are rare.

Neurological involvement may produce a wide spectrum of symptomatology—from changes in mental status to spastic paresis. Cerebrospinal fluid findings usually are normal. Although arthralgia is a prominent symptom, very little is known about the pathological changes within the joint. Only nonspecific synovitis has been found in histological studies of biopsy or autopsy specimens.

The nature of the foamy macrophages and their role in this disease have been extensively studied since Whipple's original description. In 1949 Black-Schaffer[8] first discussed the role of PAS-positive staining, characteristic of these macrophages. Later, Sieracki[9] found the macrophages to contain sickle-shaped granules. He called it the SPC cell, standing for the sickle form particle containing cells. These granules stained positively with the PAS stain. Whipple's original case was subsequently studied and also showed the typical changes of PAS-positive macrophages.

In the early 1960's two independent groups of investigators[10,11] studied tissues from patients with Whipple's disease using electron microscopy. They both reported rod-shaped bacillary bodies in the lamina propria of the small intestinal mucosa and within the macrophages. Now confirmed by many investigators, this appears to be a universal finding in active cases. By careful sectioning and staining one can see the bacilli by light microscopy as well. In fact, in his original report Dr. Whipple himself had called attention to a rod-shaped organism found in one of the lymph nodes.

A typical bacillus viewed by electron micros-

copy measures approximately 1 micron in length and 0.2 micron in diameter and has a cell wall closely applied to a typical triple-layered cell membrane. It is found to be most abundant in the extracellular spaces in the lamina propria before treatment is begun. These "bacillary" bodies have now been shown to be present in the intestinal mucosa, the mesenteric and peripheral lymph nodes, the brain and also the heart of patients with Whipple's disease. Electron microscopic studies have shown phagocytosis of these bacilli by macrophases leading to the formation of intracellular granules. The bacilli then undergo distintegration and ultimately form particles of closely packed membranous material. The particles containing these membranes are equivalent to the sickle-form particles described by Sieracki[9] and stain positively with PAS stain. They may remain for years after successful treatment, whereas the extracellular bacilli disappear within a few days after treatment has begun.

Although the bacilli are found most abundantly in the intracellular spaces and within the cytoplasm of macrophages located in the lamina propria, they have also been shown to involve the absorptive epithelial cells, and likely contribute to their diminished function. Brice and co-workers[12] have found decreased amino acid uptake and decreased capacity to reesterify free fatty acid by the intestinal mucosa from patients with Whipple's disease. Morphological changes in the intracellular organelle also suggest abnormal lipid metabolism. After a fatty meal there is normally an accumulation of lipid in the smooth endoplastic reticulum where reesterification of free fatty acid occurs. This intracellular process is decreased in patients with Whipple's disease.[3] These data suggest that this is an important contributing mechanism to fat malabsorption. This is further supported by the close correlation between functional and structural improvement following antibiotic treatment. Additional possible mechanisms of malabsorption include: a reduction in epithelial cell mass; physical impedance of chylomicron transport to the central lacteals by the presence of a great number of macrophages within the lamina propria; obstruction of lymphatic flow secondary to enlarged mesenteric nodes, and, finally, functional damage to the lymphatic endothelium.

Before the use of antibiotics, Whipple's disease was invariably fatal. In the early 1950's treatment with corticosteroids was common. Patients treated with steroids alone usually showed early clinical response, but quickly relapsed. Scattered reports of dramatic response to antibiotics then began to appear in the literature, but it was not until 1963 that Davis and associates[13] showed antibiotics to be invariably effective and that prolonged treatment was necessary to prevent relapses. They recommended therapy with penicillin, 1.2 million units, and streptomycin, 1 gram a day for ten days, followed by tetracycline, 1 gram per day for 10 to 12 months. With this regimen, no recurrence of symptomatology was observed in 12 patients.

The clinical response to therapy is dramatic and within a week patients begin to feel better and diarrhea subsides. Significant weight gain quickly follows and within six months all laboratory abnormalities will have reverted to normal. As previously mentioned, the PAS-positive macrophages may persist for many years and, therefore, are not a useful measure of improvement. The most sensitive histological change is the disappearance of extracellular bacillary bodies which generally occurs in a few days. The reappearance of these bacillary bodies heralds a relapse.[14]

Based on morphological data, and the fact that patients invariably respond to antibiotics, most investigators agree that Whipple's disease is an infectious disease. However, as yet no one has convincingly isolated the bacteria nor reproduced the disease in an animal model. Many bacteria have been isolated, but contamination has always been a possibility.

Recently isolation of an atypical bacterium from jejunal mucosa and peripheral lymph node has been accomplished.[15] On subsequent subcultures reversion back to an alpha hemolytic Streptococcus occurred. This organism appears to be a facultative intracellular parasite and its incubation with human fibroblasts causes accumulation of PAS-positive material within the cultured cells. Demonstration of serum antibodies against the bacteria has been accomplished by indirect immunofluorescence. Finally, when the organism was injected into a rabbit, a systemic disease characterized pathologically by the accumulation of PAS-positive material within macrophages developed.

Atypical bacteria have been isolated previously by other investigators. Charache and co-workers[16] isolated a bacterium from six different blood cultures and from a peripheral lymph node in a patient with Whipple's disease. The organism ini-

tially required hypertonic media for growth and took a pleomorphic form. On subsequent subcultures, however, the organism reverted back to a beta hemolytic Streptococcus and when ingested by leukocytes *in vitro,* it formed particles the same size as the bacillary bodies seen in Whipple's disease. The organism isolated by these authors was not pathogenic in mice and rabbits. These reports do not constitute conclusive proof of a cause-and-effect relationship and much more work is needed to clarify this matter.

Much has been learned about Whipple's disease since its original description, but there remain many unanswered questions. Why is it a rare disease? What is the explanation for the age and racial preferences and its striking geographic distribution? What host factors predispose to development of Whipple's disease? Several recent reports have focused on the possibility of immunologic defects. Unfortunately, most of these studies are carried out using isolated cases and it is difficult to draw meaningful conclusions from them. Although in occasional patients immunoglobulin deficiency has been shown, impaired humoral immunity is not a consistent finding. Our patient had normal immunoglobulin levels.

Aberrations in delayed cutaneous hypersensitivity have been found in patients with Whipple's disease.[14] These are associated with an *in vivo* alteration of lymphocyte function. In nine patients with treated Whipple's disease (studied at ten months to 16 years after antibiotic therapy) delayed hypersensitivity reactions were significantly depressed. Phytohemagglutinin-induced tritiated thymidine incorporation by peripheral lymphocytes cultured in autologous plasma was consistently decreased in eight patients in comparison with similar studies of 11 control subjects.[14] Further investigations are necessary to elucidate the role of impaired cellular immunity in the pathogenesis of Whipple's disease.

A new case of Whipple's disease has been presented here and the clinical and histological features of the disease discussed. Although several observations suggest an infectious cause, the organism remains obscure. Impaired cellular immunity may be a predisposing factor but its exact role in the pathogenesis of the disease remains unclear. It should be emphasized that the diagnosis of Whipple's disease can be confirmed rather easily by a per-oral biopsy study of the small intestine, yet early diagnosis is seldom made. Once the diagnosis has been established, antibiotic treatment is invariably curative.

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